## REMARKS

Previously, claims 20-41, 44 and 46-49 were pending. By the present amendment, claims 26-28 and 47 have been cancelled. Therefore, claims 20-25, 29-41, 44, 46, and 48-49 are pending. Applicants reserve the right to prosecute in a continuing application any cancelled subject matter. Claims 20 and 44 has been amended and support for this amendment can be found in Figures 7 and 8 which show administration of xenon at concentrations between about 12.5% and 50% and temperatures between about 23°C and 37°C. Claim 30 has been amended as it was duplicative of claim 29. Claim 47 has been cancelled as a result. Claim 23 has been cancelled as it is duplicative of amended claim 1.

### Examiner Interview

Applicants thank Examiners Arnold and Richter for the courtesies extended during the interviews of January 29, 2008. During the interview, Applicants proposed amending the independent claims to recite administering a sub-anesthetic amount of a gaseous xenon mixture and specific hypothermic temperatures. Applicants pointed out, and the Examiners agreed, that the references cited in the present office action did not describe administering a sub-anesthetic amount of xenon in a gaseous form. Further, Applicants pointed to the unexpected results rendered by this range of xenon concentrations and hypothermic temperatures as supported by FIGs. 7 and 8.

### Rejection of Claims Under 35 U.S.C. §112

Claims 39 and 49 stand rejected for being allegedly indefinite with respect to the term "sub-therapeutically effective amount." However, paragraph 75 of the published application describes that in an embodiment, "xenon is administered in a sub-therapeutically effective amount. In other words, the xenon is administered in an amount that would be insufficient to produce the desired therapeutic effect if administered in the absence of hypothermic conditions." Therefore, Applicants submit that the meaning of the claim term "sub-therapeutically effective amount" is clearly described in the specification and Applicants request withdrawal of this rejection.

Rejection of Claims under 35 U.S.C. §103

Claims 20-41, 44 and 46-39 stand rejected for being allegedly rendered obvious by U.S. Patent No. 5,099,834 to Fishman ("Fishman") in view of U.S. Patent No. 6,197,323 to Georgieff ("Georgieff") and Taylor et al. Pediatric Research 51(1) pgs. 13-19 (2002) ("Taylor") and Ohashi et al. Anesthesiology 2002, 96, A1291 ("Ohashi"). Applicants traverse this rejection (with respect to the currently pending claims) as a *prima facie case* of obviousness has not been made. With respect to the cancelled claims, this rejection is rendered moot.

Claims 20 and 44 recites a method of treating neonatal asphyxia by administering a specific concentration range of xenon and a specific hypothermic temperature range. In particular, claims 20 and 44 recite administering a gaseous mixture comprising xenon where the percent concentration of the xenon in the mixture is between about 12.5% and 50%, which is a sub-anesthetic concentration range.[1] Applicants submit that these ranges are not described by any of the above-cited references.

Rather, when describing a xenon concentration, Fishman describes administering concentrations of gaseous xenon necessary to induce anesthesia. For example, Fishman provides administering 60-78.5% or 60-80% of xenon to anesthetize the patient. (See col. 2, line 15-19 and 31; col. 3, line 12 and 48). Ohashi describes administering a 75% xenon concentration, which is greater than the concentration recited by claims 20 and 44. Regarding Georgieff, when providing background information on the gaseous form of xenon, Georgieff describes a xenon concentration of 70-79% to induce anesthesia (See col. 1, lines 49-54). The remainder of Georgieff is directed to administering an emulsion, and not a gaseous mixture of xenon. Therefore, none of the references that describe administering xenon, describe administering a concentration of xenon in gaseous form between about 12.5 and 50%.

Further, the combination of the claimed xenon concentration and the claimed hypothermic temperatures renders unexpected results. For example, Figure 8 in the present

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[1] See Georgieff, col. 3, line 5-7, which provides that the anesthetic concentration of xenon is around 70%.

application shows that LDH (Lactate dehydrogenase) release[2] from neuronal cells can be reduced by exposing these cells to an atmosphere containing 12.5% xenon. The magnitude of this effect depends on the experimental temperature, which affects LDH release independent from xenon as well. The natural logarithm (ln) of the release of LDH (calculated as the fraction of the release at the experimental temperature divided by the release at 37°C without xenon) at 0% and 12.5% of atmospheric xenon is plotted against the reciprocal absolute temperature (measured in Kelvin). The data point on the far left represents the LDH release at 37°C (the log of one is zero). The data points to the right show how the LDH release is diminished by decreasing the temperature (from 37°C to 23 °C) in the absence (marked control) and presence of 12.5% xenon.

When the ln of the LDH release is plotted against the reciprocal absolute temperature, the slope of the curve indicates the *enthalpy change* of the process. The enthalpy change is a measure of the heat absorbed or released at constant pressure. It indicates the extent as to which bonds are formed or broken during a process, which determines the temperature dependence of the process. The enthalpy change of -34kJ $mol^{-1}$ that was measured in the absence of xenon is typical of many biological processes. In the presence of even a sub-anesthetic concentration of xenon (12.5%), however, the enthalpy change increases enormously to -177 kJ $mol^{-1}$, which represents approximately a 420% increase. This means that the magnitude of the effect of xenon by itself on the release of LDH depends on the temperature. This is true for the entire temperature range (from about 23°C to 37°C) for which data points are available since all data points fall on a straight line.

The data in Figure 7 show that the effect of a temperature reduction from 37°C to 33°C depends on the atmospheric xenon concentration. For xenon concentrations between 12.5% and 50% by volume, this small reduction in temperature markedly increases the neuroprotection afforded by xenon.

Taken together, the data in Figures 7 and 8 show that xenon profoundly unexpectedly increases the neuroprotective effect of hypothermia and vice versa, and that these effects are seen

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[2] The release of LDH into the extracellular space is a measure of neuronal injury because LDH is usually only released from dead, but not living cells.

over the claimed temperature range of between about 23°C and 37°C and the claimed xenon concentrations of between about 12.5% and 50%. As such, taken together, Applicants' data demonstrates that the claimed methods of treating neonatal asphyxia provide unexpected results.

For at least these reasons, Applicants submit that the present claims are not rendered obvious by the cited references and Applicants request withdrawal of this rejection.

## CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Any fees for extension(s) of time or additional fees required in connection with the filing of this response, are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON LLP

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